THE FREQUENCIES OF LEFT- AND RIGHT-SIDED BREAST CANCER.

T. BUSK AND J. CLEMMESEN.

From the Danish Cancer Registry under The National Anti-Cancer League.

Received for publication October 31, 1947.

BECAUSE of the anatomical and physiological symmetry of the breasts it is generally assumed that also their pathological symmetry goes without saying—nay even without documentation.

The question whether breast cancer arises with the same frequency in both breasts became topical to one of us while examining whether relatives with breast cancer were more likely than other persons to develop their tumours of that organ on the same side.

For our examination we have used the material of hospital cases notified to The Danish Cancer Registry. We are indebted to our medical colleagues for their interest, and the result that out of 4139 female cases of carcinoma from the years 1942–46 inclusive, only 17 have not been referred to any of the two sides.

The total Danish material will naturally also include cases from private practice known to the Cancer Registry only through death certificates. Because of the difficulties involved in obtaining accurate information as to the site of the tumour in many of these cases they have been left out of the present examination. They amount to about 130 cases each year. Thus 412 cases from the years 1942–44, known only from death certificates, consisted of 81 left-sided and 64 right-sided cases, together with 7 bilateral and 260 unstated cases.

Table I gives the number of cases for each of the two sides, distributed according to age. Similar tables showing the numbers of unmarried, married, divorced and widowed persons with breast cancer have also been worked out to examine if these conditions might influence the side of the tumour. The table gives these figures for the whole period, and for each year. The sum total shows 2117 tumours of the left and 1908 of the right breast. In 97 cases tumours were stated to have occurred on both sides, while the localization of 17 tumours was unknown.

The question now arises if this surplus of 209 cases in the left breast is statistically significant or may be due to chance.

In order to test the hypothesis that left- and right-sided breast cancers occur with equal frequency, the following considerations were made :

Consider n observations of the same kind, by which the events A_1, A_2, A_3 occur with the probabilities p_1, p_2, p_3 respectively, where $p_1 + p_2 + p_3 = 1$. The probability that A_1, A_2, A_3 will occur a_1, a_2, a_3 times respectively is then according to the multinomial theorem :

$$p\left\{a_1, a_2, a_3\right\} = \frac{n!}{a_1!\, a_2!\, a_3!}\; p_1^{a_1}\, p_2^{a_2}\, p_3^{a_3}, \text{ where } a_1 + a_2 + a_3 = n.$$

If we put $p_1 = p_2 = p$ we get

$$p\left\{a_1, a_2, a_3\right\} = \frac{n!}{a_1!\, a_2!\, a_3!}\, p^{a_1 + a_2}\, (1 - 2p)^{a_3},$$

TABLE I.—*Cancer of Left and Right Breast.*

Age.	1942. L.	R.	Bilateral.	Unsp.	Total.	1943. L.	R.	Bilateral.	Unsp.	Total.	1944. L.	R.	Bilateral.	Unsp.	Total.
15–19															
20–24	1	2			3										
25–29			1		1	2				2	1	2			3
30–34	6	9	1		16	7	8			15	16	10	2		28
35–39	14	14	1		29	21	18		1	40	20	24			44
40–44	33	33	5		71	40	42		1	83	42	37	2		81
45–49	49	39	6		94	60	53	4		117	55	50	3		108
50–54	42	34	1		77	32	45	4		81	51	34	2		87
55–59	63	44	4		111	68	48	2		118	60	44	3	2	109
60–64	49	44	4	1	98	65	60	2	1	128	63	43	2		108
65–69	43	39	3		85	50	37	7		94	80	45	4		129
70–74	29	28	2		59	35	37	1		73	40	33	3		76
75–79	11	14	1		26	22	20	3	1	46	20	20	2		42
80–84	5	5			10	9	10	2	1	22	11	9			20
85–89	3	2			5	1	1	1		3	4	5			9
90–94															2
unstated														1	1
Total	348	307	29	1	685	412	379	26	5	822	464	357	23	3	847
Of which unmarried	65	57	6	1	129	82	73	7		162	95	77	12		184

Age.	1945. L.	R.	Bilateral.	Unsp.	Total.	1946. L.	R.	Bilateral.	Unsp.	Total.	1942–46. L.	R.	Bilateral.	Unsp.	Total.
15–19							2			2		2			2
20–24		1			1	1				1	2	3			5
25–29	4	2			6	4	1			5	11	5	1		17
30–34	13	13			26	7	7			14	49	47	3		99
35–39	21	20			41	32	28			60	108	104	1	1	214
40–44	49	34			83	46	40			86	210	186	7	1	404
45–49	52	44	2		98	65	60	2	1	128	281	246	17	1	545
50–54	59	62	1		122	56	56			112	240	231	8		479
55–59	63	52	3	1	119	59	60			119	313	248	12	3	576
60–64	55	69			124	58	51	2		111	290	267	10	2	569
65–69	51	63	1	2	117	53	43	6	1	103	277	227	21	3	528
70–74	36	47		2	85	29	37			66	169	182	6	2	359
75–79	15	19			34	28	26			54	96	99	6	1	202
80–84	10	14			24	12	8	2	1	23	47	46	4	2	99
85–89	6	2			8	8	4			12	22	14	1		37
90–94	1				1						2	1			3
unstated														1	1
Total	435	442	7	5	889	458	423	12	3	896	2117	1908	97	17	4139
Of which unmarried	86	94	1		181	92	96	2	1	191					

TABLE I—*continued.*

Unmarried women 1942–46.

	L.	R.	Both	Unsp.	Total.
15–19		2			2
20–24	2				2
25–29	1	1			2
30–34	10	6	2		18
35–39	19	13			32
40–44	51	50	2		103
45–49	50	65	4		119
50–54	37	49	4		90
55–59	61	56	3		120
60–64	63	54	3	1	121
65–69	52	47	4		103
70–74	39	33	3		75
75–79	18	15	2		35
80–84	13	5		1	19
85–89	4	1	1		6
90–94					
unstated					
Total	420	397	28	2	847

and by the binomial theorem we get for the probability of $(a_1 + a_2)$ events of either of the two kinds A_1 and A_2 in n observations:

$$p\left\{a_1 + a_2\right\} = \frac{n!}{(a_1 + a_2)!\, a_3!} (2p)^{a_1 + a_2} (1 - 2p)^{a_3}.$$

The probability that A_1 occurs just a_1 times in a series of n observations where just $(a_1 + a_2)$ of the results belonged to either of the groups A_1 and and A_2 is then

$$p\left\{a_1, a_2, a_3 \,\middle|\, a_1 + a_2\right\} = \frac{(a_1 + a_2)!}{a_1!\, a_2!} \left(\tfrac{1}{2}\right)^{a_1 + a_2} \tag{1}$$

This result is identical with the one obtained if n_1 observations are made with the probabilities $p_1 = \frac{1}{2}$ of the event A_1 and $p_2 = \frac{1}{2}$ of A_2 and the probability of getting the event A_1 just a_1 times is sought:

$$p\left\{a_1\right\} = \binom{n_1}{a_1} \left(\frac{1}{2}\right)^{n_1}$$

as we get the right side of (1) if we put $n_1 = a_1 + a_2 = n - a_3$.

The procedure involved in (1): by n observations $(n = a_1 + a_2 + a_3)$ to keep $(a_1 + a_2)$ at a certain fixed value is then tantamount to omitting the a_3 cases of the event A_3 and confining the considerations to the remaining $n - a_3$ observations in testing the hypothesis that A_1 and A_2 are equally frequent.

As an approximative test it can be asserted that the quantity

$$u = \frac{\frac{a_1}{n_1} - \frac{1}{2}}{\sqrt{\frac{1}{2} \cdot \frac{1}{2} \cdot \frac{1}{n_1}}} = \frac{a_1 - a_2}{\sqrt{n_1}}$$

approximately should be normally distributed with mean zero and variance 1, if $p_1 = p_2$.

For the application to the problems in question we interpret:

A_1 = tumour in the left breast;
A_2 = tumour in the right breast;
A_3 = bilateral or unstated localization of breast cancer;

and calculations then give $u = 3{\cdot}29$, corresponding to a value P of about 1 per thousand.

Assuming that the left and right breast cancer was equally frequent, calculations according to the tests described have shown that only one out of a thousand samples of the size of the present data could be expected to show a deviation equal to, or exceeding the differences observed. Thus the preponderance of left-sided breast cancer can be considered as statistically significant, and according to the present material each hundred cases of cancer in the right breast will correspond to 111 of the left.

In working out the material we found some variations in the left-side preponderance of the different years. Especially the year 1945 showed a slightly

higher frequency of right-sided tumours, and computations were therefore carried out to ascertain whether these variations would contradict the assumption of a constant inequality with regard to lateral distribution of breast cancers in all five years.

TABLE II.—*Number of Left-sided Breast Cancers per Thousand Cases with Known Localization.*

Year.	Married women, etc.	Unmarried women.	Total.
1942	531	533	531
1943	519	529	521
1944	569	552	565
1945	501	478	496
1946	528	489	520
1942–46	529	514	526
χ^2	6·59	2·73	8·50
f	4	4	4
P	>0·10	>0·50	>0·05

The χ^2 test carried out in Table II gives the value 8·50 with four degrees of freedom, and as this corresponds to $P>$ 5 per cent, it means that the material does not disprove the assumption of constant inequality in lateral distribution.

Considering the well-known differences in frequency of breast cancer among married and unmarried women, we have tested the corresponding values for breast cancer of each side for two groups, respectively of women not previously married, and of the remaining group of married, divorced and widowed women. We found for each hundred right-sided cancers, 105·8 left-sided tumours among unmarried, and 112·3 among the remaining women, and this difference between the two groups cannot be considered as significant.

TABLE III.—*Number of Left-sided Breast Cancers per Thousand Cases with Known Localization.*

Age.	Married, divorced and widowed women.						Unmarried women 1942–46.	Total 1942–46.
	1942.	1943.	1944.	1945.	1946.	1942–46.		
34	333	539	591	483	556	505	591	521
35–39	462	514	436	486	556	494	594	509
40–44	480	500	517	623	567	539	505	530
45–49	580	548	566	559	556	561	435	533
50–54	574	438	614	505	517	527	430	510
55–59	609	554	610	574	500	568	521	558
60–64	506	510	588	455	537	516	538	521
65–69	533	586	660	449	530	556	525	550
70–74	468	466	542	406	451	466	542	482
75–79	476	525	433	440	500	482	545	492
80–	538	500	423	464	583	495	739	538
All ages	531	519	569	501	528	529	514	526
χ^2	7·91	4·53	12·94	11·25	2·88	13·38	12·05	9·69
f	10	10	10	10	10	10	10	10
P	>0·50	>0·90	>0·20	>0·30	>0·98	>0·20	>0·20	>0·50

In order to examine whether the higher frequency of left-sided breast cancer varies with age, Table III has been worked out. χ^2 tests, however, revealed no significant variations.

Searching for similar materials from other countries we found a report on the Swiss cancer census from the years 1933–35 by Fellenberg (1940), giving the figures for left- and right-sided breast cancer. The total amounted to 1045 cases, of which 522 were localized to the left and 464 to the right breast ; 22 cases were bilateral and 37 without statement of side.

Computations carried out according to the methods described give a value for u of 1·85, so that, even if no statistically significant difference has been demonstrated, the tendency is nevertheless in agreement with the findings from the Danish material, and of almost the same order of magnitude. Thus for each 100 cases of cancer in the right breast we find in Denmark 111 left-sided, and in Switzerland 113 left-sided tumours.

It is outstanding that out of the total surplus of 58 left-sided cases, 50 are found in the material from Zurich, but the application of the χ^2 test shows that this may be due to chance alone.

Our attention has been called to the fact that in his Statistical Review for 1935 (p. 86) the Registrar-General of England and Wales analysed the deaths from breast cancer in 1931–34 as follows :—

	R.	*L.*	*Bilateral.*	*Unspecified.*
Males	30	33	—	7
Females	2623	2995	643	269

and commented that cancer of the left breast was more frequently certified than cancer of the right breast to the extent of 14 per cent. The proportion of bilateral cases is much greater than in the Danish material, as might be expected, since they consist only of fatal cancers. If *total* occurrences in right and left breasts are compared after adding the bilateral cases to the numbers for each side, the left-sided excess becomes 11 per cent, which is the same as the author's find from the Danish data.

Table IV quotes the report of Janet E. Lane-Claypon (1926), examining the effect of injury to the breast on the frequency of cancers respectively of the same and the opposite breast.

TABLE IV.—*Figures According to Janet Lane-Claypon.*

Type of injury to the breast.	Tumour in the—	Number of cases with injury to—				Computed value of u.
		Left breast.	Right breast.	Both sides.	Side unstated.	
Injury and bruising	Same breast	29	12	..	..	2·66
,, ,,	Opposite breast	1	1	..	..	..
Injury, no bruising	Same ,,	50	39	..	..	..
Injury doubtful	,, ,,	2	4	..	..	..
Slight injury	,, ,,	20	21	..	..	..
Injury and bruising	No tumour	5	2	1	2	..
Injury, no bruising	,,	7	6	..	5	..
Slight injury	,,	2	1	..	2	..
Total (slight inj. excl.)	..	92	60	1	7	2·60

It is seen that in this material also the left breast shows more cancers than the right. However, concerning the coincidence of injury with cancer, the figures are too small to permit any direct comparisons of the two sides.

Application of the tests described gives the result that injuries seem to occur more frequently to the left than to the right breast. This applies both to the cancer patients separately and to the total material, and thus it follows that cancers coinciding with injury are more frequent in the left than in the right breast.

Considering the pretexts for the development of cancer in the two breasts, it does not seem unreasonable to suppose that the different incidence demonstrated may be connected with difference in use of the upper extremities, for instance by lactation or by protection against injury. But whether the differences in injuries sustained by the breasts has any connection with the difference in cancer incidence, or is a mere coincidence, nobody can tell at present.

SUMMARY.

Among 4139 female cases of breast cancer notified from hospitals to The Danish Cancer Registry, 2117 tumours were localized to the left and 1908 to the right breast, while 97 were bilateral and 17 without statement of side.

Applying a special test the authors demonstrated that, provided cancer frequency of the two breasts were the same, only one out of a thousand samples of the size investigated could be expected to show a deviation equal to, or exceeding the difference observed.

Smaller materials from Switzerland, 1935, and England, 1926, show similar features. Thus for each 100 cases of cancer in the right breast we find in Denmark 111 left-sided, and in Switzerland 113 left-sided tumours. The English material shows a higher frequency of injury to the left than to the right breast.

REFERENCES.

FELLENBERG, R. v.—1940. "Schweiz. Erhebung über maligne Tumoren." *Bull. Eidgenöss. Gesundheitsamt, Bern.*

LANE-CLAYPON, J. E.—(1926). 32 ' Rep. Minist. Hlth. Lond., p. 156.